(19) Japanese Patent Office
(12) **Publication of Unexamined Patent Application**
(11) Disclosure Number: **Hei 4-41421**
(43) Disclosure Date: 1992.02.12
(51) International Patent Classification:
A61K 9/12
9/08
9/107
37/02
37/26
47/12
Examination request status: not yet requested
Number of Claims: 3
Total Pages: 4
(54) Title of the Invention: Pulmonary Absorbable Composition
(21) Filing Number: Hei 2-149545
(22) Date of Application: 1990.06.07
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Specifications

1. Title of the Invention

Pulmonary Absorbable Composition

2. Scope of the Patent Claims

[Claim 1] A pulmonary absorbable composition; the pulmonary absorbable composition being in aqueous solution or powder form; the pulmonary absorbable composition being manufactured by blending of

(A) one or two or more compounds selected from a group comprising: proteins, peptides and derivatives thereof; and

(B) an aqueous solution adjusted to have a pH of 3 to 4, or in the case of a powder, a powder adjusted to have a pH of 3 to 4 when dissolved in water;

and / or a surfactant.

[Claim 2] The pulmonary absorbable composition of Claim 1; wherein insulin is included as a peptide.

[Claim 3] The pulmonary absorbable composition of Claim 1 or Claim 2; wherein citric acid is used to adjust the aqueous solution to a pH of 3 to 4, or in the case of a powder, used for adjustment so that an aqueous solution of the powder has a pH of 3 to 4.

3. Detailed Explanation of the Invention

[Industrial Field of Application]

The present invention relates to a pulmonary absorbable composition containing a protein or peptide or derivative thereof.

[Earlier Technology and Problem to be Solved by the Invention]

In recent years, many bioactive peptides, proteins, or derivatives thereof have been produced in large volume in accompaniment with advances in peptide synthesis and genetically engineering methods, and many such compounds are being clinically used as peptide-type pharmaceuticals or protein-type pharmaceuticals. However, since these peptides and proteins have extremely low body-penetrability and readily undergo oxidative decomposition, except for a few such compounds, administration is limited to subcutaneous injection, intramuscular injection, or intravenous injection. Therefore non-injection type forms of administration are strongly desired in order to make these new-technology type pharmaceuticals widely used in the future.

[Means to Solve the Problems]

As a result of research concerning simple and immediately effective pulmonary administration of proteins and peptides, the inventors of the present invention discovered that when a protein, peptide, or derivative thereof in the presence of various types of surfactants beginning with glycocholic acid, or as an aqueous solution at a pH of 3 to 4, is administered, the protein, peptide, or derivative thereof is quickly adsorbed into the body, and concentration of the protein or peptide in the blood rapidly rises. The present invention was attained based upon this discovery.

That is to say, the present invention is a pulmonary absorbable composition; the pulmonary absorbable composition being in aqueous solution or powder form; the pulmonary absorbable composition being manufactured by blending of

(A) one or two or more compounds selected from a group comprising: proteins, peptides and derivatives thereof; and

(B) an aqueous solution adjusted to have a pH of 3 to 4, or in the case of a powder, a powder adjusted to have a pH of 3 to 4 when dissolved in water;

and / or a surfactant.

The protein, peptide, or derivative thereof of the present invention is derived from an animal, is synthesized, or is obtained by genetic engineering methods, including chemical modification of compounds obtained by such methods. The form of administration of the pulmonary absorbable composition of the present invention is preferably an aerosol composition containing the protein, peptide, or derivative thereof; a dispersing agent or aqueous solution; and an aerosol propellant.

A surfactant may be used as the surfactant of the present invention if the main pharmaceutical agent is not adversely affected thereby. A surfactant used as a nebulizing agent for various types of pharmaceutical agents can be used. Examples that can be suggested of preferred surfactants include sorbitan monooleate, glycerin monostearate, sorbitan monopalmitate, sorbitan monolaurate, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate, etc. A particularly preferred example of the surfactant is sorbitan triolate (Span 85).

Any pH adjustment agent can be utilized as the adjustment agent used for pH 3 to 4 adjustment if the pH adjustment agent does not adversely affect the main pharmaceutical agent. Although any pH adjustment agent can be utilized that is used within general pharmaceutical compositions, a particularly preferred pH adjustment agent that can be suggested is citric acid.

When water is used, such water is purified water, distilled water for injection use, etc. In this case, the obtained composition is an aqueous aerosol preparation.

The content of the above mentioned type of surfactant in such water may be in the range of 0.1 to 5 wt%.

Although various types of pharmaceutically permissible gases can be used as the aerosol propellant, preferred aerosol propellants that can be suggested include trichlorofluoromethane, dichlorotetrafluoroethane, dichlorodifluoromethane, and mixtures thereof.

[Results of the Invention]

By means of the present invention, a peptide or derivative thereof can be quickly absorbed into the body upon pulmonary administration, and peptide concentration within the blood quickly rises. By this means, although a peptide formerly required subcutaneous injection, intramuscular injection, or intravenous injection, administration of this peptide becomes possible without pain of injection and the inconvenience of a hospital visit.

[Working Examples]

The present invention will be explained next by presentation of specific working examples and test examples.

Working Example 1

First 5 mg of human insulin, 40.7 mg of citric acid, and 4.3 mg of sodium citrate were ground in a mortar down to 1 - 5 μm particle size under a dry nitrogen gas purge. Then 100 mg of sorbitan triolate was added and uniformly blended in. This powder and 6 g of a 2: 3 mixture of trichlorofluoromethane and dichlorofluoromethane were charged into a pressure-resistant container. A metering spray valve was attached to obtain an aerosol preparation.

Working Example 2

First 5 mg of human insulin was dissolved in a pH 3 citric acid - sodium citrate buffer solution to obtain 4 mL total solution volume. This was charged into a pressure-resistant container together with 1.4 g of a 3 : 2 mixture of dichlorodifluoromethane and dichlorotetrafluoroethane. A metering spray valve was attached to obtain an aerosol preparation.

Test Example 1

Under anesthesia, 10 μL of insulin aqueous solution (3 U/kg) was administered to a rat via a tracheotomy opening. Blood insulin concentration was measure by the EIA method at one hour intervals.

[Results]

Results are shown in **Figure 1**.

Bioavailability was markedly increased by use together with Span 85 surfactant or glycocholic acid as shown in **Figure 1**.

Test Example 2

Testing was carried out by the Test Example 1 method. pH of the aqueous solution was varied and insulin absorption from the lungs was measured.

[Results]

As shown in **Figure 2**, bioavailability was increased 3-fold when the administered insulin aqueous solution pH was 3 in comparison to administration of pH 7 insulin aqueous solution.

However, a pH below 3 is undesirable due to lung tissue damage by the acidic solution.

4. Simple Explanation of the Illustrations

Figure 1 shows a comparison (versus subcutaneous injection) of the effect of various types of absorption promoters on the pulmonary absorption of insulin.

Figure 2 shows observed blood insulin concentrations as pH of an administered insulin solution was varied.

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Figure 1. Effect of various types of absorption promoters on pulmonary absorption of insulin.

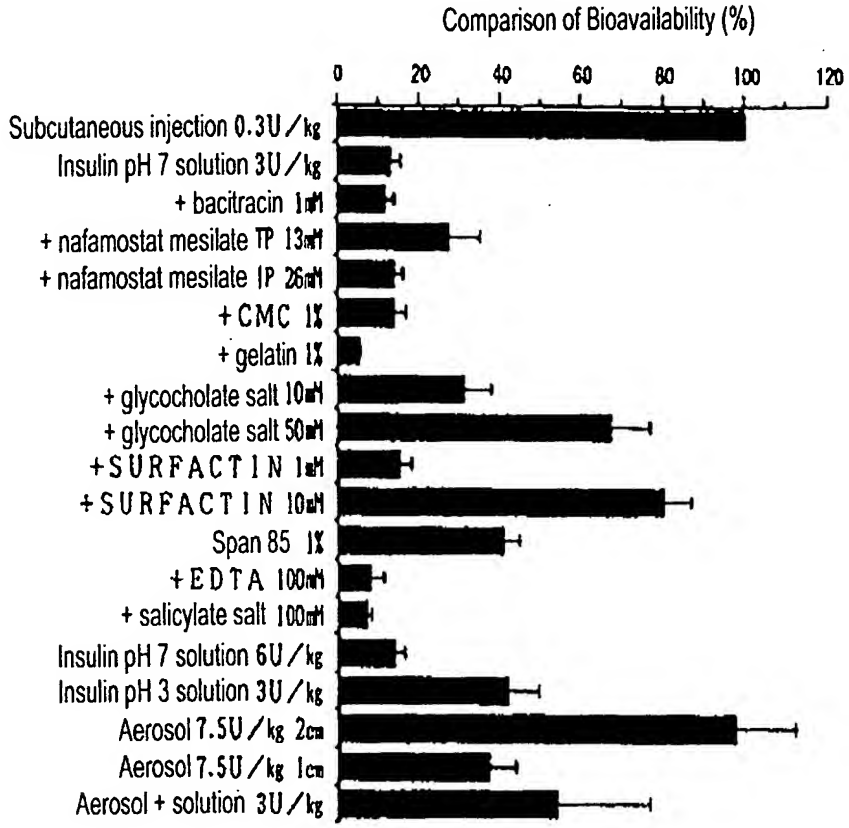

Figure 2. Effect over time of pH on concentration in blood of pulmonary administered insulin.